REMARKS

Claims 1-9 and 25-29 are pending. Claims 10-24 were previously canceled. Claims 7-9 and 27 have been withdrawn by the Examiner as drawn to nonelected species. Applicant respectfully reminds the Examiner that upon finding allowable subject matter, applicant is entitled to have the withdrawn claims rejoined and considered in this application as provided by 37 C.F.R. 1.141. *See* M.P.E.P. § 809.02(a). Claims 1-6, 25, 26, 28, and 29 are under consideration.

Applicant notes, with appreciation, the withdrawal of the rejection of claims 1-6, 25, 26, 28, and 29 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-9, 20, 35, 37, 39, 41, and 43 of copending U.S. Application No. 10/744,844. Action at page 2, item no. 3.

Applicant also acknowledges, with appreciation, the Examiner's withdrawal of the rejection of claims 1-6, 25, 26, 28, and 29 under § 103(a) as allegedly being unpatentable over Kumpel et al., Hum. Antibod. Hybridomas 5:143-151 (1994) ("Kumpel") in view of U.S. Patent No. 5,834,251 issued to Maras et al. ("Maras"). Action at page 3, item no. 5.

Rejection of Claims 1-6, 25, 26, 28, and 29 Under 35 U.S.C. § 103(a)

The Examiner newly rejected claims 1-6, 25, 26, 28, and 29 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 4,859,449 issued to Mattes ("Mattes"), in view of Kumpel and Maras. Action at page 3, item no. 6.

In the Examiner's view, Mattes teaches therapeutic antibodies with terminal galactose oligosaccharides and the uses/advantages of such antibodies. The Examiner acknowledges that

Mattes does not teach that the antibodies are of the degree of purity recited in the claims. Nevertheless, the Examiner alleges that

> [i]t would have been prima facie obvious to one of ordinary skill in the art to have created the claimed invention because Mattes teaches therapeutic antibodies with terminal galactose oligosaccharides and the uses/advantages of such antibodies whilst Kumpel teach that antibodies with substantially all G2 oligosaccharaide have increased lysis of target cells in comparison to the same antibody which is produced in a manner that results in low levels of G2 and Maras et al teach that B-1,4 Galactosyltrasferase can be used to modify the oligosaccharide profile on a glycoprotein. . . .

Action at p. 3-4.

Applicant respectfully traverses the rejection. As explained further below, there is simply no teaching or suggestion in Mattes of "[a] therapeutic composition comprising a glycoprotein preparation, said glycoprotein having an immunoglobulin CH2 domain said CH2 domain having at least one N-linked oligosaccharide wherein substantially all of the oligosaccharide is a G2 oligosaccharide and wherein the amount of said glycoprotein containing G1 and G0 oligosaccharide does not exceed 10% by weight of the preparation," according to claim 1. The Examiner has failed to establish a *prima facie* case of obviousness.

Mattes is directed to methods of modifying antibodies for therapeutic and diagnostic purposes such that they are cleared more rapidly from the circulation. *See, e.g.*, Mattes at abstract and col. 2, lines 3-17. According to Mattes, such antibodies are "conjugated to, or [have] exposed thereon, a plurality of terminal glycoside residues which bind to the human hepatocyte asialoglycoprotein receptor." Mattes at col. 2, lines 37-39.

While Mattes does discuss that one may "expos[e] such glycosides as terminal residues on existing, complex carbohydrates on the antibody," and notes that such "glycosides can be exposed on the surface of an antibody by suitable treatment," e.g., by using neuraminidases (*See, e.g.*, col. 6, lines 21-26 and at lines 47-57), this is <u>not recommended</u> for the <u>therapeutic</u> methods

described in Mattes. Significantly, Mattes warns that "neuraminidase-mediated desialylation does not always result in sufficient exposure of lectin-binding glycoside residues on an antibody." *Id.* at lines 65-67. Thus, to address this perceived limitation to the practice of the described therapeutic methods, Mattes discusses at length various methods for **attaching glycosides** to proteins including preferred methods using amidination (*see, e.g.*, col. 7, line 23 – col. 8, line 8), a process specifically exemplified in the prophetic examples at cols. 13-14.

Importantly, such methods for **attaching glycosides** are used to produce antibodies having "a plurality of conjugated glycoside residues. . . . Preferably, at least about 10 glycoside residues per antibody/fragment will be sufficient for accelerated clearance, more particularly at least about 25 residues for rapid clearance, and perhaps more for still more rapid clearance, e.g., up to about 50-75 residues per antibody/fragment." Col. 8 at lines 30-37 (emphasis added). Thus, contrary to the Examiner's assertion, Mattes does not teach or suggest that "G2 antibodies have the maximum number of terminal galactose oligosaccharides" and would have the therapeutic uses/advantages described in the specification. Rather, Mattes describes that such G2 antibodies are undesirable for the therapeutic methods described therein and that it is preferable to **attach additional glycosides** to antibodies so that each antibody will have 10-25 glycoside residues and even as many as 50-75 glycoside residues. The Examiner will no doubt appreciate that these numbers of glycoside residues/antibody far exceed the number of glycoside residues present in a "G2 antibody" of the claims.

Accordingly, not only does Mattes fail to teach or suggest the claimed "glycoprotein having an immunoglobulin CH2 domain said CH2 domain having at least one N-linked oligosaccharide wherein substantially all of the oligosaccharide is a G2 oligosaccharide and wherein the amount of said glycoprotein containing G1 and G0 oligosaccharide does not exceed

10% by weight of the preparation," it actually teaches away from the invention of the present claims, at least because it emphasizes the importance to the therapeutic methods of Mattes of attaching additional glycosides to antibodies in numbers that are far greater than that found on a G2 oligosaccharide of the present claims. Such teaching away is noteworthy because, as provided in the MPEP, "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP § 2141.02(VI). Moreover, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." MPEP § 2143.01(III). "A prior art reference that 'teaches away' from the claimed invention is a significant factor to be considered in determining obviousness. . . ." MPEP § 2145(X)(D)(1). Accordingly, the invention of the present claims would not have been obvious to one skilled in the art in view of Mattes.

Likewise, as discussed at length in the previous response filed on September 8, 2008, which is incorporated by reference in its entirety, neither Kumpel or Maras, alone or in combination teach or suggest "[a] therapeutic composition comprising a glycoprotein preparation, said glycoprotein having an immunoglobulin CH2 domain said CH2 domain having at least one N-linked oligosaccharide wherein substantially all of the oligosaccharide is a G2 oligosaccharide and wherein the amount of said glycoprotein containing G1 and G0 oligosaccharide does not exceed 10% by weight of the preparation," according to claim 1. In fact, as discussed at length in the prior response, each of Kumpel and Maras teaches away from the claimed invention emphasizing, e.g., the desirability of antibodies having "glycosylation profiles that were similar to the average value for normal serum IgG," (Kumpel) and "glycosylation patterns similar to those found proteins from higher eukaryotes" (Maras). Mattes

fails to cure the deficiencies of Kumpel and/or Maras for at least the reasons explained fully above. The Examiner has therefore not established a *prima facie* case of obviousness.

There is simply no teaching or suggestion in any one of Mattes, Kumpel or Maras of "[a] therapeutic composition comprising a glycoprotein preparation, said glycoprotein having an immunoglobulin CH2 domain said CH2 domain having at least one N-linked oligosaccharide wherein substantially all of the oligosaccharide is a G2 oligosaccharide and wherein the amount of said glycoprotein containing G1 and G0 oligosaccharide does not exceed 10% by weight of the preparation," according to claim 1. Furthermore, there is simply no motivation to combine Mattes with Kumpel and/or Maras or to modify those documents as proposed by the Examiner especially given that each of the cited documents teaches away from the claimed invention. Accordingly, claim 1 would not have been obvious in view of Mattes, Kumpel and/or Maras. Each of claims 2-6, 25, 26, 28, and 29 ultimately depend from claim 1 or otherwise include all the elements of claim 1. Therefore, none of the dependent claims would have been obvious in view of Mattes, Kumpel and/or Maras. Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-6, 25, 26, 28, and 29 under 35 U.S.C. § 103(a) as allegedly being obvious in view of Mattes, Kumpel and/or Maras.

Because the Examiner fails to establish that claims 1-6, 25, 26, 28, and 29 would have been obvious for at least the reasons discussed above, Applicant need not address the Examiner's contentions concerning other elements of those claims. By not addressing those contentions, applicant in no way acquiesces to those contentions.

CONCLUSION

Applicant respectfully asserts that the claims are in condition for allowance and requests the timely issuance of a Notice of Allowance. Should the Examiner believe that a telephone

interview would expedite the prosecution of this application, applicant invites the Examiner to call the undersigned at the telephone number indicated below.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 07-0630.

Respectfully submitted,

GENENTECH, INC.

Dated: April 22, 2010

By: _____

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